Express Mail Label No. EV 326 983 429 US Attorney Docket No. 55600-8014.US00


**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICATION OF:
Liu & Villarete

APPLICATION NO.: 10/824,710

FILED: April 14, 2004

FOR: **METHOD OF TREATMENT USING INTERFERON-TAU**

EXAMINER: Unassigned

ART UNIT: Unassigned

## PETITION TO MAKE SPECIAL

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with 37 CFR § 1.102 and the procedure set forth in MPEP §708.02, section VIII, for accelerated examination procedure, the applicant requests, prior to examination, that the above-identified application be granted special status.

The applicant submits that the present petition and accompanying documents meet all of the requirements set forth at MPEP §708.02, section VIII. Specifically, the applicant hereby submits the following:

(a) the present petition to make special, accompanied by the fee set forth in 37 CFR 1.17(i) ($130.00);

(b) a preliminary amendment intended to limit the claims in the application to a single invention;

(c) a statement that a pre-examination search was made by applicant's agent, listing the field of search; and

(d) a detailed discussion of the references deemed most closely related to the subject matter encompassed by the claims, which points out, with the particularity

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required by 37 CFR § 1.111 (b) and (c), how the claimed subject matter is distinguishable over the references.

The applicant requests that, if the present request is defective in any respect, the applicant be given an opportunity to perfect the request, as provided in MPEP §708.02, section VIII.

The Commissioner is authorized to charge any underpayment of fees herein (or credit any overpayment) to Deposit Account No. 50-2207.

Respectfully submitted,

Judy McL

Date: May 7, 2004

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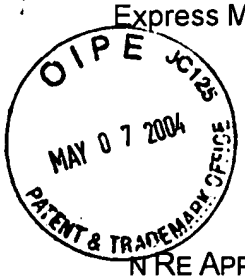


**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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## STATEMENT REGARDING PREEXAMINATION SEARCH IN CONNECTION WITH PETITION TO MAKE SPECIAL

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Judy M. Mohr, an authorized agent in the above-identified application, hereby declare that a pre-examination search has been made in accordance with to MPEP §708.02, section VIII, in the following databases and with the following search queries:

A. Searches Performed and References Submitted

The World Patent Index and Medline were each searched, with separate search queries directed to:

(a) interferon tau (hereinafter IFNτ or IFN-tau) plus oral delivery or administration;

(b) interleukin-10 (hereinafter "IL-10") or IL-10 plus interferon.

From these searches, the U.S. patents and published applications, foreign patents and applications, and journal publications listed in the attached IDS Form 1449 were selected for review.

Copies of the references discussed herein are enclosed herewith and are listed in the current Form 1449.

B. Discussion of the Art

**B1. Patents and Published Patent Applications Related to Oral Administration of IFNτ**

1. U.S. Patent No. 6,372,206 for "Orally-Administered Interferon-tau Compositions and Methods", issued April 16, 2002, filed March 15, 1996.
2. US 2003/0012766 for "Orally-Administered Interferon Tau Compositions and Methods ", published Jan. 16, 2003, filed Dec. 21, 2001.
3. PCT Patent Application No. PCT/US97/03794 for "Orally-Administered Interferon Tau Compositions and Methods ", published September 18, 1997 as WO 97/33607, filed March 12, 1997.

Remark Concerning Patentability of Instant Claims in view of Documents 1-3: This family of patent documents discloses oral administration of IFNτ for treatment of a variety of conditions, including autoimmune disorders, such as multiple sclerosis, viral infection and cancer. The documents do not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor do the teachings in the documents show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor do the documents show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

4. U.S. Patent No. 6,060,450 for "Method for Treatment of Autoimmune Diseases", issued May 9, 2000, filed May 25, 1999.
5. U.S. Patent No. 5,906,816 for "Method for Treatment of Autoimmune Diseases", issued May 25, 1999, filed March 16, 1995.
6. PCT Patent Application No. PCT/US96/03472 for "Method for Treatment of Autoimmune Diseases Using Interferon-tau", filed March 15, 1996.

Remark Concerning Patentability of Instant Claims in view of Documents 4-6: This family of patent documents discloses oral administration of IFNτ for treatment of autoimmune disorders. The documents do not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor do the teachings in the documents show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor do the documents show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

7. PCT Patent Application No. PCT/US93/10016 for "Interferon Tau Compositions and Methods of Use", filed October 19, 1993.
8. U.S. Patent No. 5,958,402 for "Antitumor Therapy Using Ovine or Bovine Interferon-tau", issued September 28, 1999, filed May 31, 1995.
9. U.S. Patent No. 5,705,363 for "Recombinant Production of Human Interferon-τ Polypeptides and Nucleic Acids", issued Jan. 6, 1998, filed May 10, 1995.
10. US 2002/0013452 for "Interferon Tau Compositions and Methods of Use", published Jan. 31, 2002, filed Dec. 22, 2000.

Remark Concerning Patentability of Instant Claims in view of Documents 7-10: This family of patent documents discloses administration of IFNτ for treatment of a variety of conditions. The references suggest administration of IFNτ by oral administration among a variety of modes of administration, however they do not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor do the teachings in the documents show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor do the documents show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

11. PCT Patent Application No. PCT/US90/01122 for "Composition for the Inhibition of Tumors and for the Non-Cytotoxic Inhibition of Replication of Viruses", filed March 1, 1990.

Remark Concerning Patentability of Instant Claims in view of Document 11: This publication discloses administration of IFNτ to inhibit viral activity and tumor formation. The reference suggests administration of IFNτ by oral administration among a variety of modes of administration, however it does not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor does the teaching in the document show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor does the document show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

12. US 2003/0130486 for "Hybrid Interferon/Interferon Tau Proteins, Compositions and Methods of Use", published July 10, 2003, filed Aug. 12, 2002.

Remark Concerning Patentability of Instant Claims in view of Document 12: This publication discloses administration of an interferon/interferon-tau hybrid protein, where the C-terminus of interferon-alpha is replaced with corresponding residues from interferon-tau. The document does not show or suggest administering IFNτ, nor does the document disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U.

13. US 2003/0049277 for "Composition for Treatment of and Method of Monitoring Hepatitis C Virus Using Interferon Tau ", published March 13, 2003, filed July 19, 2001.

Remark Concerning Patentability of Instant Claims in view of Document 13:
The present application claims priority to this application, removing the document as effective prior art.

14. US 2003/0219405 for "Oral Administration of Interferon Tau ", published Nov. 27, 2003, filed Jan. 16, 2003.

Remark Concerning Patentability of Instant Claims in view of Document 14:
The present application has a priority date of July 19, 2000. Thus, document 14 is not available as prior art.

15. US 2004/0013643 for "Method for Treatment of Multiple Sclerosis with Statins", published Jan. 22, 2004, filed Jan. 22, 2003.

Remark Concerning Patentability of Instant Claims in view of Document 15:
The present application has a priority date of July 19, 2000. Thus, document 15 is not available as prior art.

16. U.S. Patent No. 6,083,919 for "Materials and Methods for Treating Autoimmune Disease", issued July 4, 2000, filed Dec. 5, 1997.
17. U.S. Patent No. 6,403,562 for "Materials and Methods for Treating Autoimmune Disease", issued June 11, 2002, filed July 27, 1999.

Remark Concerning Patentability of Instant Claims in view of Documents 16-17:
These related patents disclose treating autoimmune disorders with a combination therapy that includes IFNτ as the second treatment agent. The references suggest administration of IFNτ by oral administration among a variety of modes of administration, however they do not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor do the teachings in the documents show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration.

Nor do the documents show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

18. U.S. Patent No. 6,036,949 for "Treatment of Fibromyalgia with Low Doses of Interferon", issued March 14, 2000, filed March 5, 1998.

Remark Concerning Patentability of Instant Claims in view of Document 18:
This patent describes treating of fibromyalgia with low doses, e.g., on the order of 1-1500 U per day, of interferon orally. The teaching does not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor does the teaching in the documents show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor does the document show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

19. PCT Patent Application No. PCT/IB00/01080 for "Interferon Tau Mutants and Methods for Making Them", published December 28, 2000, filed June 22, 2000.

Remark Concerning Patentability of Instant Claims in view of Document 19:
This publication describes mutants of IFNτ for treatment of a variety of conditions. The reference suggests administration of IFNτ by oral administration among a variety of modes of administration, however it does not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor does the teaching in the document show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration. Nor does the document show or suggest continuing to administer such an effective dose despite changes in measurable IL-10 blood levels.

**B2. Journal Articles Related to Oral Administration of IFNτ**

20. Soos, J.M. *et al.,* "Oral Feeding of interferon tau can prevent the acute and chronic relapsing forms of experimental allergic encephomyelitis," *J. Neuroimmunology*, 75:43-50 (1997).

    Remark Concerning Patentability of Instant Claims in view of Document 20: This paper describes oral feeding of ovine IFNτ to mice to block development of experimental allergic encephomyelitis (EAE), a model for multiple sclerosis. Mice were treated with $10^5$ U of IFNτ, administered from various concentrations of IFNτ: $10^5$ U/mL, 2 x $10^5$ U/mL, or 5 x $10^5$ U/mL. The paper does not show or suggest a dosage of IFNτ for human subjects that would be effective to induce IL-10.

21. Soos, J.M. *et al.,* "Cutting Edge: Oral Type I IFN-τ Promotes a Th2 Bias and Enhances Suppression of Autoimmune Encephalomyelitis by Oral Glatiramer Acetate," *J. Neuroimmunology*, 169(5):2231 (2002).

    Remark Concerning Patentability of Instant Claims in view of Document 21: This paper was published in 2002, after Applicants' priority date and is not effective prior art.

22. Nakajima, A. *et al*, "Induction of Blood 2',5'-Oligoadenylate Synthetase Activity in Mice by Gastric Administration of Ovine IFN-τ," *J. Interferon and Cytokine Research*, 22:397-402 (2002).

    Remark Concerning Patentability of Instant Claims in view of Document 22: This paper was published in 2002, after Applicants' priority date and is not effective prior art.

23. Khan, O.A. *et al*, "Immunomodulation Functions of Recombinant Ovine IFN-: Potential for Therapy in Multiple Sclerosis and Autoimmune Disorders," *Mult. Scler.*, 4(2):63 (1998).

Remark Concerning Patentability of Instant Claims in view of Document 23: This paper examines the *in vitro* toxicity of ovine IFNτ when applied to cells in culture at a concentration of up to $10^7$ U/mL. The paper does not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor does the teaching in the document show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration.

24. Mujtaba M.G. *et al*, "IFN-τ Suppresses Both the Autoreactive Humoral and Cellular Immune Responses and Induces Stable Remission in Mice with Chronic Experimental Allergic Encephalomyelitis" *Cell Immunol.*, 186(2):94 (1998).

Remark Concerning Patentability of Instant Claims in view of Document 24: Mujitaba *et al.* describe oral administration of ovine IFNτ to mice at a dose of $6 \times 10^5$ U. The paper does not disclose or suggest administering IFNτ at a daily dosage of greater than $5 \times 10^8$ U. Nor does the teaching in the document show or suggest that IFNτ when administered at such dosages would be effective to produce a measurable increase in the subject's serum IL-10 level, relative to the IL-10 level in the subject in the absence of IFNτ administration.

**B3. Journal Articles Related to Characteristics of IFNτ**

25. Soos, J.M. *et al.*, "Type I Interferon Inhibition of Superantigen Stimulation: Implications for Treatment of Superantigen-Associated Disease," *J. Interferon and Cytokine Research*, 15:39-45 (1995).

Remark Concerning Patentability of Instant Claims in view of Document 25: This paper describes the ability of type I interferons to inhibit the activity *in vitro* of staphylococcal enterotoxin superantigens. Cells were treated with interferon doses of $10^5$ U (Table 3) and show to be effective inhibitors of cell proliferation.

The paper does not show or suggest oral administration of IFNτ at a dose of greater than 5 x $10^8$ U.

26. Pontzer, C.H. *et al.,* "Antiproliferative Activity of a Pregnancy Recognition Hormone, Ovine Trophoblast Protein-1," *Cancer Research*, 51:5304 (1991).

Remark Concerning Patentability of Instant Claims in view of Document 26:
This paper describes the antiproliferative activity of ovine IFNτ. Cells were treated *in vitro* with concentrations of IFNτ of up to 5 x $10^4$ Units/mL. The paper does not show or suggest oral administration of IFNτ at a dose of greater than 5 x $10^8$ U or that administration of IFNτ orally will induce IL-10.

27. Pontzer, C.H. *et al.,* "Antiviral Activity of the Pregnancy Recognition Hormone, Ovine Trophoblast Protein-1," *Biochem. Biophys. Research Comm.*, 152(2):801 (1988).

Remark Concerning Patentability of Instant Claims in view of Document 27:
This paper reports that ovine IFNτ (ovine trophoblast protein-1) has antiviral activity. The paper does not show or suggest oral administration of IFNτ at a dose of greater than 5 x $10^8$ U or that administration of IFNτ orally will induce IL-10.

28. Alexenko, A.P. *et al.,* "The Antiproliferative and Antiviral Activities of IFN-τ Variants in Human Cells," *J. Interferon Cytokine Res.*, 17:769 (1997).

Remark Concerning Patentability of Instant Claims in view of Document 28:
This paper compares the antiviral and antiproliferative activities of a series of bovine and ovine IFNτ mutants. The paper does not show or suggest oral administration of IFNτ at a dose of greater than 5 x $10^8$ U or that administration of IFNτ orally will induce IL-10.

**B4. Journal Articles Related to Interferon-alpha and Interfereon-beta**

29. Brod, S.A., "Autoimmunity Is a Type I Interferon-Deficiency Syndrome Corrected by Ingested Type I IFN via the GALT System," *J. Interferon Cytokine Res.*, 19:841 (1999).

Remark Concerning Patentability of Instant Claims in view of Document 29:
This paper describes ingestion of IFNα and IFNβ to generate an immune response via gut associated lymphoid tissue. On page 847, col. 2, Brod notes that ovine IFNτ has been reported to have activity when given orally at high doses of $10^5$ U, but anti-IFNτ antibodies blocked the effect of IFNτ. The paper does not show or suggest oral administration of IFNτ at a dose of greater than $5 \times 10^8$ U or that administration of IFNτ orally will induce IL-10.

30. Brod, S.A. *et al.*, "Ingested Interferon α Suppresses Type I Diabetes in Non-Obese Diabetic Mice," *Diabetolotgia*, 41:1227 (1998).

Remark Concerning Patentability of Instant Claims in view of Document 30:
This paper describes that oral administration of 10 U IFNα to mice inhibits insulinitis and suppresses Type I diabetes mellitus. The paper does not show or suggest oral administration of IFNτ at a dose of greater than $5 \times 10^8$ U or that administration of IFNτ orally will induce IL-10.

31. Brod S.A. *et al.*, "Oral Administration of Human or Murine Interferon Alpha Suppresses Relapses and Modifies Adoptive Transfer in Experimental Autoimmune Encephalomyelitis," *J. neuroimmunology*, 58:61 (1995).

Remark Concerning Patentability of Instant Claims in view of Document 31:
This paper describes oral administration of between 10-1,000 U of murine IFNα or 100-1,000 U of human IFNα to mice. The paper does not show or suggest oral administration of IFNτ at a dose of greater than $5 \times 10^8$ U or that administration of IFNτ orally will induce IL-10.

**B5. Journal Articles Related to Cytokine Level and Multiple Sclerosis**

32. van Boxel-Dezaire, A.H.H. *et al.,* "Decreased Interleukin-10 and Increased Interleukin-12p40 mRNA Are Associated with Disease Activity and Characterize Different Disease Stages in Multiple Sclerosis," *Annals of Neurology*, 45(6):697 (1999).

Remark Concerning Patentability of Instant Claims in view of Document 32: This paper describes the correlation between express of certain cytokines and disease state in multiple sclerosis patients. The paper does not show or suggest oral administration of IFNτ at a dose of greater than $5 \times 10^8$ U or that administration of IFNτ orally will induce IL-10.

33. Makhlour, K. *et al*, "Increased percentage of IL-12+ monocytes in the blood correlates with the presence of active MRI lesions in MS," *J. Neurological Sciences.*, 119:145 (2001).

Remark Concerning Patentability of Instant Claims in view of Document 33: This paper describes the relationship between blood 1L-12 level and disability stage of multiple sclerosis patients. The paper does not show or suggest oral administration of IFNτ at a dose of greater than $5 \times 10^8$ U or that administration of IFNτ orally will induce IL-10.

Respectfully submitted,

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Registration No. 38,563

Date: May 7, 2004

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